sis, were not associated with the incidence of left atrial appendage thrombus.
Conclusions: Maintenance hemodialysis patients have left atrial appendage thrombus at an unexpectedly high incidence. The chronic use of antiplatelet drugs and the concomitant presence of diabetes mellitus and a low hematocrit may be involved in left atrial appendage thrombus formation.

1008-130 Comparison of Echocardiographic Indices of Right Ventricular Obstruction in Pulmonary Embolism

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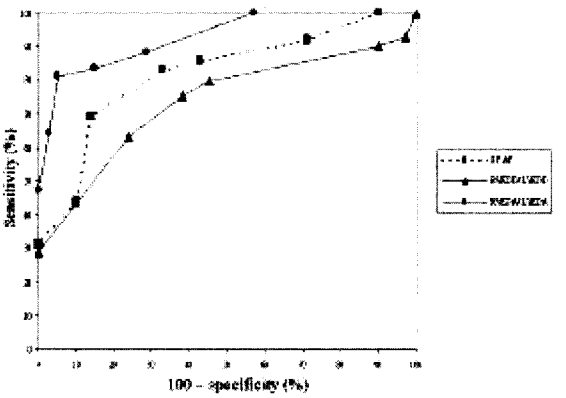
Background: Different echocardiographic parameters have been described in pulmonary embolism (PE). The purpose of this study was to determine the most accurate echocardiographic index of right ventricular obstruction in acute PE.
Methods: Fifty-seven consecutive patients (mean age 56 ± 17 years) presenting with PE quantified by angiographic Miller index were studied. Following echocardiographic parameters were systematically assessed: 1) right to left ventricular end-diastolic diameter ratio (RVEDD/LVEDD) in parasternal long-axis view, 2) right to left ventricular end-diastolic area ratio (RVEDA/LVEDA) in apical 4-chamber view, 3) systolic pulmonary arterial pressure (SPAP) using CW Doppler.
Results: The correlations between echocardiography and Miller index were 0.52 for the RVEDD/LVEDD, 0.72 for the RVEDA/LVEDA and 0.52 for SPAP. Using Miller index higher than 40% to define massive PE with echocardiographic disorders, the cut-off values of the RVEDD/LVEDD, the RVEDA/LVEDA and SPAP that yielded the highest discriminating power were 0.5, 0.6 and 35 mmHg respectively, according to ROC curves. Echocardiographic ROC curves analysis showed that the RVEDA/LVEDA was the more accurate indicator of right ventricular obstruction.
Conclusion: This echocardiographic study suggests that the right to left ventricular end-diastolic ratio using apical four-chamber view is the most accurate echocardiographic parameter of right ventricular obstruction in acute PE, with a ratio higher than 0.6.



1008-131 Bosentan Increases Warfarin Dosing Requirements in Pulmonary Hypertension

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Background: Bosentan is the first oral agent to have proven effectiveness in pulmonary arterial hypertension. Warfarin also has proven benefits and is used in most patients with this condition. Data from a trial in healthy volunteers have suggested that bosentan can reduce prothrombin time in those taking warfarin. This is the first study examining the effect of bosentan on the International Normalising Ratio (INR) in any patient population.
Methods: A retrospective observational study was performed of 19 warfarinised patients with pulmonary hypertension who had been enrolled in an open label bosentan study. 10 of the patients had primary pulmonary hypertension, 4 had chronic thromboembolic pulmonary hypertension, 3 had scleroderma and 2 had systemic lupus erythematosis. Their mean age was 40 years. The patients had their INR and warfarin dose recorded at baseline, after a month of bosentan at a dose of 62.5 mg twice daily, and after an additional month at a dose of 125 mg twice daily.Warfarin doses were adjusted at the discretion of the patients' general practitioners with a target range of 2-3.
Results: There was an increase in the mean warfarin dose from 3.8 (SD 1.4) to 4.4 (SD 1.5) after a month on the low bosentan dose and a further increase to 4.8 (SD 1.5) after a month on the higher dose. This increase was statistically significant ($p<0.01$). The corresponding INRs were 2.5 at baseline, 2.6 after 1 month and 2.5 after 2 months. These were not significantly different.
Conclusion: When warfarinised patients with pulmonary hypertension are started on bosentan, they require a higher dose of warfarin to maintain a steady INR.

1008-132 The Utility of Sildenafil in Infants With Pulmonary Hypertension

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Background: The treatment of pulmonary artery hypertension (PAH) has been limited by the paucity of effective and affordable oral therapy. The use of sildenafil in adults with PAH has been reported. However, its efficacy in the pediatric population has not been fully evaluated. We used it as a last resort in 3 infants with pulmonary hypertension and the results are reported.
Methods: Infants with PAH unresponsive to conventional therapy available at our center were considered for sildenafil therapy. Parental consent was obtained in accordance with the hospital protocol for investigational drugs. The clinical status and echocardiographic indicators of PAH such as tricuspid regurgitation (TR) jet gradient and the direction of the patent ductus arteriosus (PDA) were assessed. As we were using an investigational drug as a 'last-ditch' effort, cardiac catheterization data was not obtained. Sildenafil was started and echo evaluation repeated at 24 hours, 48 hours and 1 week.
Results: Between March to August 2002, 3 infants at our institution had severe PAH requiring therapeutic intervention. The age range was 15 days to 9 months and weight was 2.5 to 6.5 kg. The diagnoses included a postoperative PDA ligation (n=1) and 2 infants with persistent primary pulmonary hypertension with no identifiable cardiac cause. In 2 infants the TR jet gradient decreased from 75-80 to 20-30 mmHg within 24 hours of starting sildenafil, and the patients were rapidly weaned off the ventilator and oxygen. In the 9 month old no response was noted initially or at 1 week.
Conclusion: Oral sildenafil appears to be especially effective in neonates with pulmonary hypertension. If it works, the effect appears to be dramatic and occurs within 24-48 hours. Further prospective trials to assess its effect, and decide on dosing schedules, are needed.

1008-133 Survival After Diagnosis of Primary Pulmonary Hypertension: Single Center Experience With Transplantation and Preoperative Therapy With Prostacyclin Analogues

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Background: Without treatment, patients with primary pulmonary hypertension (PPH) survive less than 3 years after diagnosis. Our study summarized over 11 years clinical experience in PPH therapy.
Methods: We reviewed our institution's experience with both transplantation (Tx) and preoperative prostanoid therapy. The analysis included all PPH patients (58 women, 27 men) referred by our institution for Tx between 1991 and 2002. Tx was performed in 36 of these patients (21 heart-lung and 15 double-lung Tx). Since 1996 we used a stepwise therapeutic regimen which included beraprost tablets or iloprost inhalation in the earlier stages of the disease and intravenous iloprost infusion in NYHA class IV patients.
Results: The actuarial survival since diagnosis for all 85 evaluated patients was 90.5% at 1 year, 69.4% at 3 years, 62.5% at 10 years, and the mean survival time since diagnosis was 138 ± 17 months. Of these patients, only 15 underwent neither vasodilator therapy with prostanoids (for various reasons) nor transplantation (8 patients died before Tx, 7 are still on the waiting list). The other 70 were treated with prostanoids or with transplantation or with both. The actuarial survival after PPH diagnosis in this group reached 74.1% at 3 years and 66.7% at 10 years. The 3 year actuarial survival since diagnosis was 78.4% in patients treated preoperatively with prostanoids and 56.25% in those without prostanoids. The mortality rate on the waiting list for Tx was 11.5% in the prostanoid group and 28.1% in the group without prostanoid treatment. The actuarial post-transplant survival was 44.5% at 5 years and 42.9% at 8 years. At the present time, 27 patients are being treated with prostanoids. Listing for transplantation could be postponed during this treatment of 25.2 ± 12,6 months duration in 26 patients, although the mean time since diagnosis reached already 58.0 ±54.4 months.
Conclusions: Since use of prostanoids increases the 3-year actuarial survival after PPH diagnosis and reduces the mortality rate on the waiting list, it is an effective bridging-to-transplant therapy. Transplantation in combination with prior prostanoid administration provides important survival benefits for PPH patients.

POSTER SESSION

1009 Variations in Clinical Response to Antiplatelet and Anticoagulant Agents

Sunday, March 30, 2003, 9:00 a.m.-11:00 a.m.
McCormick Place, Hall A
Presentation Hour: 9:00 a.m.-10:00 a.m.

1009-117 Clopidogrel Nonresponders Discovered During Point-of-Care Platelet Aggregation Testing

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Background: The phenomenon of aspirin resistance has recently been recognized. During the course of determining that cytochrome P450 (CYP) 3A4 is the primary catalyst for the metabolic activation of the prodrug clopidogrel, it was observed that the effectiveness of a loading dose of clopidogrel varied in healthy volunteers.

Methods: Platelet aggregation was measured with the point-of-care MICROS™ cell counter (ABX Diagnostics, Irvine, CA) and the Plateletworks™ test platform (Helena Laboratories, Beaumont TX) using 20 μM ADP agonist in 20 human healthy volunteers before any drug administration (0 hours) and 4 hours following clopidogrel 450 mg oral administration. Subjects with percent platelet aggregation ≥ 70% at 4 hours after clopidogrel administration were considered to be non-responders. Subjects with percent platelet aggregation < 70% at 4 hours after clopidogrel administration were considered to be responders. *In vivo* CYP3A4 activity at baseline and 4 hours after clopidogrel was measured by the erythromycin breath test. Results were compared using a two group t-test.

Results: Twenty-five percent (5/20) of the subjects did not respond to a loading dose of clopidogrel. Platelet aggregation was significantly higher in the non-responders as compare with the responders 4 hours after clopidogrel administration (80 ± 9% vs. 37 ± 20%, p=0.0002). The metabolic activity of CYP3A4 in the clopidogrel non-responders was lower than in the responders (1.9 ± 0.7% vs. 2.7 ± 1.0 % $^{14}CO_2$ exhaled/hour, p=0.15).

Conclusion: This study demonstrates that clopidogrel non-responders exist and that they have lower metabolic activity of CYP3A4. These results, in addition to our previous observation that atorvastatin and potentially other CYP3A4 substrates attenuate the platelet inhibitory activity of clopidogrel, amplifies the importance of determining whether platelet aggregation inhibition targets are being met in individual patients by point-of-care platelet aggregation testing.

1009-118 Effects of Clopidogrel-Aspirin Combination Versus Aspirin Alone on Platelet Aggregation and Major Receptor Expression in Patients With Heart Failure: For the Plavix Use for Treatment of Congestive Heart Failure (PLUTO-CHF) Trial

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Background: Persistent platelet activation may contribute to thrombotic events in patients with congestive heart failure (CHF). Chronic use of platelet inhibitors could therefore represent an independent avenue to improve morbidity, mortality, and quality of life in this expanding population. We assessed antiplatelet properties of clopidogrel with aspirin (C+A) versus aspirin alone (A) in CHF patients with heightened platelet activity.

Methods: Patients with LVEF < 40%, or CHF symptoms in the setting of preserved systolic function and NYHA Class II-IV were screened. Patients were considered to have platelet activation when 4 out of the following 5 parameters were met: ADP- induced platelet aggregation>60%; collagen-induced aggregation >70%; whole blood aggregation>18 ohms; expression of GP IIb/IIIa> 220 log MFI; and P-selectin cell positivity > 8%. All patients received aspirin 325 mg for at least a month prior to screening. Patients were randomly assigned to C+A (n=25), A (n=25) groups, or represent screen failures (n=36). Platelet studies were performed at baseline and after 30 days of therapy.

Results: There were no deaths, hospitalizations, or serious adverse events. There were no changes in platelet parameters in the A group. In contrast, therapy with C+A resulted in a significant inhibition of platelet activity assessed by ADP- (p=0.00001), and epinephrine-induced (p=0.0016) aggregation, closure time (p=0.04), expression of PECAM-1 (p=0.009), GP Ib (p=0.006), GP IIb/IIIa antigen (p=0.0001), GP IIb/IIIa activity with PAC-1 (p=0.0021), CD151 (p=0.0026) when compared with A group. Therapy with C+A also resulted in the reduced formation of platelet-leukocyte microparticles (p=0.021). Collagen-induced aggregation in plasma and in whole blood, expression of vitronectin receptor, P-selectin, CD63, CD107a, and CD107b did not differ between groups.

Conclusion: Treatment with C on top of the ASA provides greater inhibition of platelet activity than aspirin alone in CHF patients. Patients with CHF exhibiting heightened platelets represent a potential target population in which addition of clopidogrel may decrease mortality by reducing incidence of thrombotic vascular events.

1009-119 Whole Blood Aggregometry as a Potential Method of Detecting Aspirin Resistance

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Background: Much attention has currently being given to the phenomenon of aspirin resistance as a potential cause of therapeutic failure for patients taking this agent. Despite this attention, little is known regarding factors that may predispose to aspirin resistance and how to identify aspirin-resistant patients.

Methods: We studied 13 healthy volunteers (mean + s.d. age = 25.5 + 5.9 years) in an open-labeled study. Each subject received a single oral 325 mg dose of aspirin. Blood samples were drawn at 0, 5, 10, 15, 20, 25, 30, 45, 60, 75, and 90 minutes and at 2, 4, 6, 8, 12, 24, 48, and 72 post-dose to determine the onset of duration of aspirin effect. Platelet aggregation was assessed at each time point using whole blood impedance aggregometry with collagen (1.0 mcg/mL) and arachidonic acid (0.5 mM) as pro-aggregants. The onset of aspirin effect was defined as at least 25% inhibition of aggregation compared to baseline. The duration of aspirin effect was defined as a return of platelet aggregation to 75% of baseline.

Results: The onset of aspirin effect was within 30 minutes for 9 subjects and within 90 minutes for all subjects in response to collagen. In response to arachidonic acid, the onset of effect was within 30 minutes for 12 subjects and within 45 minutes for all subjects. By 24 hours, the aspirin effect had worn off in 2 subjects in response to collagen and in 2 additional subjects by 48 hours post-dose. Inhibition of platelet aggregation in response to arachidonic acid persisted throughout the 72-hour study in all patients.

Conclusion: Whole blood aggregometry may prove to be a useful tool in detecting aspirin resistance. Using this method, we have determined that a 24-hour dosing interval may be insufficient in maintaining the antiplatelet effects of aspirin in a significant number of patients. In these patients, twice daily dosing of aspirin may be needed to maintain therapeutic efficacy. Future studies are needed in patients with cardiovascular disease to identify the prevalence of aspirin resistance in this population.

1009-152 Demographic and Clinical Predictors of Excessive Anticoagulation Following Initiation of Warfarin Therapy

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Background: Anticoagulant therapy with warfarin has established efficacy in the prevention of thromboembolic events. However, its potential benefits are limited by the risk of excessive anticoagulation and subsequent serious or fatal hemorrhage. We sought to identify patient characteristics that predict excessive international normalized ratio (INR) response after initiation of a uniform warfarin dosing regimen. **Methods:** Among patients (pts) in the Coumadin Aspirin Reinfarction Study (CARS) who were randomized to treatment with warfarin 3mg daily, excessive INR response was defined as INR >4.0 after one week of therapy. The dose of warfarin was fixed, and INR measurements were performed at the end of first week of therapy by a core laboratory using the same thromboplastin reagent (International Sensitivity Index, ISI=0.97). A logistic regression model was used to assess the relationship of baseline characteristics with excessive INR response. **Results:** Out of 2,980 treated pts, 167 (5.6%) had an INR >4.0. Pts with excessive INR had significantly lower body weight or were older, of Asian ethnicity, or on fibrate therapy. Blacks had a much lower risk of excessive INR than other races.

Variable	p	Odds Ratio (95% Confidence Interval)
Weight	0.0001	1.18 (1.12, 1.25) for 10 lbs decrease
Asian	0.0001	5.06 (2.51, 10.19)
Age	0.0001	1.36 (1.17, 1.59) for 10 years increase
Black	0.019	0.094 (0.013, 0.68)
Fibrate therapy	0.048	2.44 (1.01, 5.92)

Conclusion: These findings identify important patient characteristics that are predictive of excessive anticoagulation despite modest doses of warfarin and emphasize the recognition of high-risk clinical features. Such individuals may require more intensive monitoring and counseling during warfarin therapy.

1009-153 Unpredicted Amiodarone and Warfarin Interaction at the 17th to 20th Week After the Initiation of Amiodarone

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Background: Amiodarone and warfarin interact and warfarin dose is reduced when amiodarone is initiated. Whether further adjustments in warfarin dosage can be anticipated is unclear.

Objective: To determine whether and when adjustment of warfarin dosage after initiation of amiodarone is needed.

Method: We retrospectively reviewed Anticoagulation Clinic patients who initiated amiodarone while on warfarin therapy to determine the timing of amiodarone and warfarin interactions. INR readings were analyzed for 40 weeks after initiation of amiodarone. INRs >5.0 were defined as Grade I interactions; INR > upper target but < 5.0 were defined as grade II interactions.

Results: Of 524 patients, 24 had amiodarone started while on warfarin. Fourteen had their warfarin dose reduced when amiodarone was started. After the initiation of amiodarone, Grade I or II INR elevations were observed in 47% (41/87) of clinic visits during the first 8 weeks and 53% (20/38) from the 17th week to 20th week. There were 8%(7/87) grade 1 interactions observed during the first 8 weeks and 13% (5/38) Grade I interactions from week 17th to week 20th (see figure).

Conclusions: Amiodarone and warfarin interaction was bimodal with peaks in INR during the first two months and during the 17th-20th weeks after initiation of amiodarone. In addition to warfarin dose adjustment during initiation of amiodarone, more frequent INR checks may also be necessary 17 to 20 weeks later.